PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Resolution of dl-(3-Trifluoromethylphenoxy)-(4-Chlorophenyl)Acetic Acid

We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with (3-trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid, which is claimed in the specification of our copending Application No. 10206/65 (Serial No. 1098111).

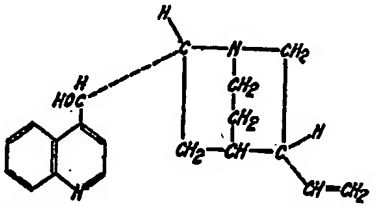
Racemic (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid and its dextro and levo isomers are hypocholesterolemic agents which effectively reduce the concentration of cholesterol in blood serum and, therefore, ameliorate conditions associated with blood lipid deposition.

In addition to their pharmacological activity racemic (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid and its dextro and levo isomers are chemical intermediates which may be converted by conventional means, as described and claimed in the specification of our copending Application No. 44020/67 (Serial No. 1182007), to various esters and amide derivatives which also exhibit hypocholesterolemic activity.

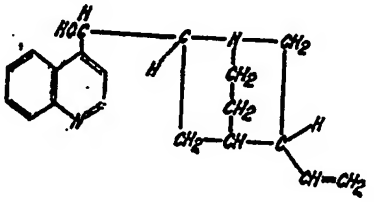
Much difficulty has been encountered in the attempted resolution of racemic (3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid. Many conventional resolving agents, such as cinchonine alkaloid, form gums with the racemic acid, thus making isolation and purification of the dextro and levo isomers a practical impossibility. In addition, the resolution of racemic (3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid is complicated by the presence of the trifluoromethyl group on the nucleus of the phenoxy radical since it increases the solubility of the diastereo isomeric salts in polar solvents. If the *d* and *l* isomers of the racemic acid are to be obtained in any substantial degree of purity, it is necessary to use a resolving agent which forms relatively insoluble salts in conventional polar solvents.

Furthermore, the use of brucine as a resolving agent is highly unpractical inasmuch as it is a relatively expensive item, at times difficultly available and, from the standpoint of safety, quite toxic in its effects.

It has now been found that, although cinchonine which has the structural formula:



reacts with racemic (3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid to yield a gum, cinchonidine, an isomer of cinchonine, having the formula:



[*Price 5s. 0d.*]

forms easily isolable crystalline salts with the *d* and *l* isomers.

In accordance with the present invention, racemic (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid is resolved by treating racemic (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid with cinchonidine to form crystalline *d* - (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid cinchonidine salt, separating the salt from the liquor and treating the said salt with acid to obtain pure (*d* - (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid; precipitating *l*-(3-trifluoromethylphenoxy) (4 - chlorophenyl)-acetic acid cinchonidine salt from the liquor by allowing the solution to stand for a protracted period, and treating the said salt with acid to obtain *l* - (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid. The salts are preferably washed with a suitable alcohol, e.g. a C_{1-6} alkanol such as methanol, ethanol or isopropyl alcohol, before treatment with the acid, which is conveniently sulfuric acid. The free dextro and levo isomers of (3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid can be purified by recrystallization from methylcyclohexane.

The process of the present invention is particularly useful for the selective isolation of pure dextro isomer from racemic (3-trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid inasmuch as the *d*-(3-trifluoromethylphenoxy) 4-chlorophenyl)acetic acid cinchonidine salt immediately precipitates out of solution as a crystalline material, whereas the 1 - (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid cinchonidine salt remains in solution and must be allowed to stand for a protracted period before precipitation will occur.

The following Examples illustrate the resolution method of this invention.

Example 1

d-(3-Trifluoromethylphenoxy) (4-chlorophenyl)acetic acid

Step A:

d-(3-Trifluoromethylphenoxy) (4-chlorophenyl)acetic Acid, Cinchonidine Salt

dl - (3 - Trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid (100 g., 0.303 mole) and cinchonidine alkaloid (89.3 g., 0.303 mole) are added to 2000 ml. of isopropyl alcohol at room temperature. Crystallization of the salt begins in a few minutes. The temperature is then raised to reflux (83°C) and the mixture is cooled ambiently to 55°C, whereupon it is aged for two hours. The crystalline material that results is collected, washed with 200 ml. of hot isopropyl alcohol and dried to yield 110 g. of crude cinchonidine salt, m.p. 204—206°C. (The mother liquor thus obtained is used in Example 2, Step A, for the preparation of *l*-(3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid). The crude cinchonidine salt is slurried with 2000 ml. of ethyl alcohol and 400 ml. of methyl alcohol at reflux and then stirred and cooled ambiently overnight. After collection by filtration and washing with 200 ml. of ethyl alcohol, the product is air-dried at 60°C. to a constant weight of 69.2 g., m.p. (dec.) 213—214°C., $[\alpha]_D$ −30.2° (c=0.5 in methyl alcohol). Recrystallization of 58 g. from 1800 ml. of ethyl alcohol yields 43.1 g. of pure *d* - (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid cinchonidine salt, m.p. (dec.) 216—217° C., $[\alpha]_D$ −29.8° (c=0.5 in methyl alcohol).

Step B:

d-(3-Trifluoromethylphenoxy) (4-chlorophenyl)acetic Acid

The *d* - (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid cinchonidine salt (7.1 g.) of Step A is added to a mixture of 200 ml. of ether, 200 ml. of water and 4 ml. of concentrated sulfuric acid. The layers are separated and the ether solution is washed three times with 200 ml. of water. After drying, the ether solution is evaporated and the oil is crystallized from 25 ml. of methylcyclohexane to yield 2.95 g. of *d*-(3-trifluoromethylphenoxy (4-chlorophenyl)acetic acid, m.p. 98—100.5°C., $[\alpha]_D$ +95.3° (c=0.5 in methyl alcohol).

Example 2

l-(3-Trifluoromethylphenoxy) (4-chlorophenyl)acetic Acid

Step A:

l-(3-Trifluoromethylphenoxy) (4-chlorophenylacetic Acid, Cinchonidine Salt

The mother liquor from the crude *d*-(3-trifluoromethylphenoxy) (4 - chlorophenyl)-acetic acid cinchonidine salt isolated in Example 1, Step A, is heated to effect complete solution and then cooled ambiently. The small amount of solid which is present at 30°C. is removed by filtration, the clear filtrate is stirred at room temperature overnight and the crystalline precipitate thus obtained is collected by filtration and washed with 200 ml. of isopropyl alcohol to yield 58.8 g. of *l* - (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid, cinchonidine salt, m.p. (dec.) 200—201°C., $[\alpha]_D$ −94.7° (c=0.5 in methyl alcohol). The product (43.8 g.) is recrystallized from isopropyl alcohol (800 ml.) to give 37.3 g. of pure *l*-(3-trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid cinchonidine salt, m.p. (dec.) 200.5—201.5° C., $[\alpha]_D$ −95.5° (c=0.5 in methyl alcohol).

Step B:

l-(3-Trifluoromethylphenoxy) (4-chlorophenyl)acetic Acid

Pure *l* - (3 - trifluoromethylphenoxy) (4 -

chlorophenyl)acetic acid, cinchonidine salt (5.9 g.) from Step C is converted in essentially the same manner as described in Step B for the corresponding *d*-acid, to pure *l*-(3-trifluoromethylphenoxy) (4 - chlorophenyl) acetic acid, 2.7 g., m.p. 98—100°C., $[\alpha]_D$ −99° (c=0.5 in methyl alcohol).

WHAT WE CLAIM IS:—

1. A process for obtaining separately the *d* and *l* isomers of (3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid, which comprises treating racemic (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid with cinchonidine to form crystalline *d*-(3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid cinchonidine salt, separating the salt from the liquor and treating the said salt with acid to obtain pure *d* - (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid; precipitating *l* - (3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid cinchonidine salt from the liquor by allowing the solution to stand for a protracted period and treating the said salt with acid to obtain *l* - (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid.

2. A process as claimed in claim 1 in which the *d* - (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid, cinchonidine sale is purified by washing with a C_{1-6} alkanol.

3. A process as claimed in claim 1 or 2 in which the 1-(3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid cinchonidine salt is purified by washing with a C_{1-6} alkanol.

4. A process as claimed in any one of claims 1—3 in which the acid is sulfuric acid.

5. A process for the selective separation of pure *d*-(3-trifluoromethylphenoxy) (4-chlorophenyl)acetic acid from a racemic mixture of its optical isomers, which comprises treating racemic (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid with cinchonidine to form crystalline *d* - (3 - trifluoromethylphenoxy) (4-chlorophenyl)acetic acid, cinchonidine salt, separating the salt from the liquor, washing the said salt with a C_{1-6} alkanol and treating the salt with acid to obtain pure *d*-(3 - trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid.

6. A process as claimed in claim 5 in which the C_{1-6} alkanol is isopropyl alcohol.

7. A process as claimed in claim 5, in which the C_{1-6} alkanol is ethanol.

8. A process as claimed in claim 5, 6 or 7, in which the acid is sulfuric acid.

9. A process as claimed in claim 1, substantially as hereinbefore described in Example 1 or 2.

10. *d* - (3 - Trifluoromethylphenoxy) (4 - chlorophenyl)acetic acid when obtained by a process as claimed in any one of claims 5—8.

11. *d* or *l* - (3 - Trifluoromethylphenoxy) (4-chlorophenyl)acetic acid, when obtained by a process as claimed in any one of claims 1—4.

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